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CORRESPONDENCE

Letters to the Editor

Efficacy and Safety in Clinical Trials

In their rebuttal to my essay "Efficacy and Safety in Clinical Trials in Cardiovascular Disease" (1), Granger and McMurray (2) fired a series of rockets that missed the target.

To criticize previously identified so-called disease markers (premature ventricular complexes, cardiac output, symptom relief, plasma norepinephrine) because they do not track with disease progression is misdirected, because we all agree these are not fundamental to the disease process. As I have stressed, and Granger and McMurray seem to agree, structural markers are far more discriminating. To suggest that not all therapies that slow disease progression improve outcome is equally disingenuous; that is why I have stressed that safety as well as efficacy must be addressed.

Granger and McMurray avoid the real issue. Our treatments are aimed at slowing or aborting a disease process, but they are administered to individuals whose well-being is also dependent on other factors. Granger and McMurray seem interested only in the net effect. I am interested in separating efficacy from safety. They defend against such attempts, stating that "using measures of disease progression . . . [should be] rigorously resisted."

Rather than hiding behind their self-proclaimed inability to "understand the disease" or "the exact mechanism of benefit," Granger and McMurray would better serve the cardiovascular community by advocating that mechanisms be carefully addressed in future clinical trials so as to gain such understanding. Documentation of the benefit of therapies for early stages of disease requires assessment of disease progression, and strategies for management of advanced disease may require separate and perhaps individualized optimization of efficacy and safety. It is time to accelerate the learning process, not to retreat into the past comfort of simple mortality/morbid events trials.

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2. Granger C, McMurray J. Using measures of disease progression to determine therapeutic effect: a sirens' song. J Am Coll Cardiol 2006;48:434–7.

Reply

We were pleased to see that Dr. Cohn (1) accepts the need to examine the effect of treatment on mortality, although he chooses to see this as a measure of safety rather than efficacy. We do not know how to decide which surrogate measure "tracks with disease progression." Dr. Cohn currently favors a structural marker—a few years ago, norepinephrine or ejection fraction might have been the popular choice. Who is to say that in a few more years structural changes will go the same way as those previous favorites? Moreover, some highly effective treatments (like implantable cardioverter-defibrillators) do not affect structure or the disease process but do reduce mortality, underscoring the limitations of predicting treatment effect with disease markers.

Dr. Cohn's vision is, of course, utopian. If only we could do what he wanted—but we have not yet managed to do so and have failed miserably when we have tried. In the end, however, we agree with Dr. Cohn's call to design trials to better understand disease process and individual response to therapy. He rightly points out that our ultimate goal of individualized medicine will require much better understanding of patient response and safety. In doing so, however, even larger trials will be necessary, and ultimately measuring important clinical outcomes will always be necessary to determine the net effect that defines what matters in clinical care.

In the meantime, as long as Dr. Cohn accepts the need for assessment of "safety," the debate is more of a philosophical than practical one—the same large trials with the same clinical outcomes will be needed.

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Clinical Implications of the PROTECT–TIMI-30 Trial

We would like to congratulate Gibson et al. (1) for the completion of the recently reported PROTECT–TIMI-30 (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI